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‘Approach to’ concise clinical review

Approach to dengue fever

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ABSTRACT

Dengue fever is a significant public health concern in tropical and subtropical regions. Its global burden has risen rapidly in recent years, with climate change driving its geographic expansion, including into parts of Europe. A systemic and dynamic disease, dengue follows a clinical course comprising febrile, critical, and recovery phases. Patients exhibiting warning signs—such as persistent vomiting, abdominal pain, and lethargy—are at higher risk of developing severe dengue, primarily due to severe plasma leakage and, less commonly, severe haemorrhage or organ impairment. The disease typically presents as an acute febrile illness, often with overlapping features of other tropical infections such as chikungunya, Zika, leptospirosis, rickettsiosis, typhoid fever, and malaria, complicating early diagnosis. Point-of-care detection of the nonstructural protein 1 antigen is valuable during early illness, whereas IgM and IgG serology aids diagnosis as the disease progresses. In the absence of specific therapeutics, management focuses on symptomatic relief, judicious fluid administration, and risk stratification to identify the 3–5% of patients who may progress to severe disease. Prevention relies on vector control and, more recently, vaccination, yet gaps remain in effective antivirals, host-directed therapies, and validated biomarkers. A thorough understanding of dengue pathophysiology and its dynamic progression is essential for robust case management to reduce morbidity and mortality.

Incidence and clinical relevance

Dengue fever is the most prevalent arboviral infection worldwide, with an estimated 390 million infections annually [1,2]. It is caused by the dengue virus (DENV), a Flavivirus transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, which thrive in urban tropical and subtropical regions [3].

Driven by climate change, urbanization, globalization, and inadequate vector control, dengue incidence has risen sharply over the past three decades, placing a significant strain on healthcare systems in low- and middle-income countries [4–7]. The annual global economic burden of dengue was estimated at USD 8.9 billion in 2013 [8]. Its societal impact is also evident in Malaysia, where each symptomatic infection results in 7–9 workdays and 3–4 school days lost [9].

Over half of the world’s population across more than 100 countries is at risk of dengue infection [2] (Fig. 1). Asia, particularly South and Southeast Asia, has historically borne the greatest burden, accounting for approximately 70% of global symptomatic infections in 2010, followed by Latin America and the Caribbean [1,10]. Recognizing the scale of its impact, dengue was listed by the WHO among the top ten global health threats in 2019, alongside antimicrobial resistance and climate change [11].

By 2024, the global dengue situation had escalated markedly, with the world reporting its highest number of cases in a single year, exceeding 14.6 million cases and over 12 000 dengue-related deaths. The Region of the Americas saw an unprecedented dengue outbreak with 13 million cases, with Brazil reporting over 10 million cases and nearly 80% of deaths [2,12]. Dengue is no longer confined to the tropics. Rising global temperature, rainfall, and humidity have expanded *Aedes* mosquito habitats and facilitated dengue emergence in nonendemic regions such as France, Italy, and Spain, which together reported 308 locally transmitted cases in 2024 [2].

These global dengue trends underscore the need to strengthen surveillance, vector control, vaccination, and clinical preparedness across endemic and newly emerging regions.

Clinical presentation

Dengue is a systemic and dynamic disease. Approximately 75% of infections are asymptomatic, whereas symptomatic cases typically manifest as an acute, self-limiting febrile illness. Approximately 3–5% progress to severe dengue, of which 1–5% may be fatal [2,3,13]. After a 5–7-day incubation period, symptomatic dengue usually begins abruptly and progresses through three distinct clinical phases: febrile, critical, and recovery [14] (Fig. 2).

Febrile phase

The febrile phase, lasting 2–7 days and associated with dengue viraemia, is characterized by sudden high-grade fever, headache, retro-

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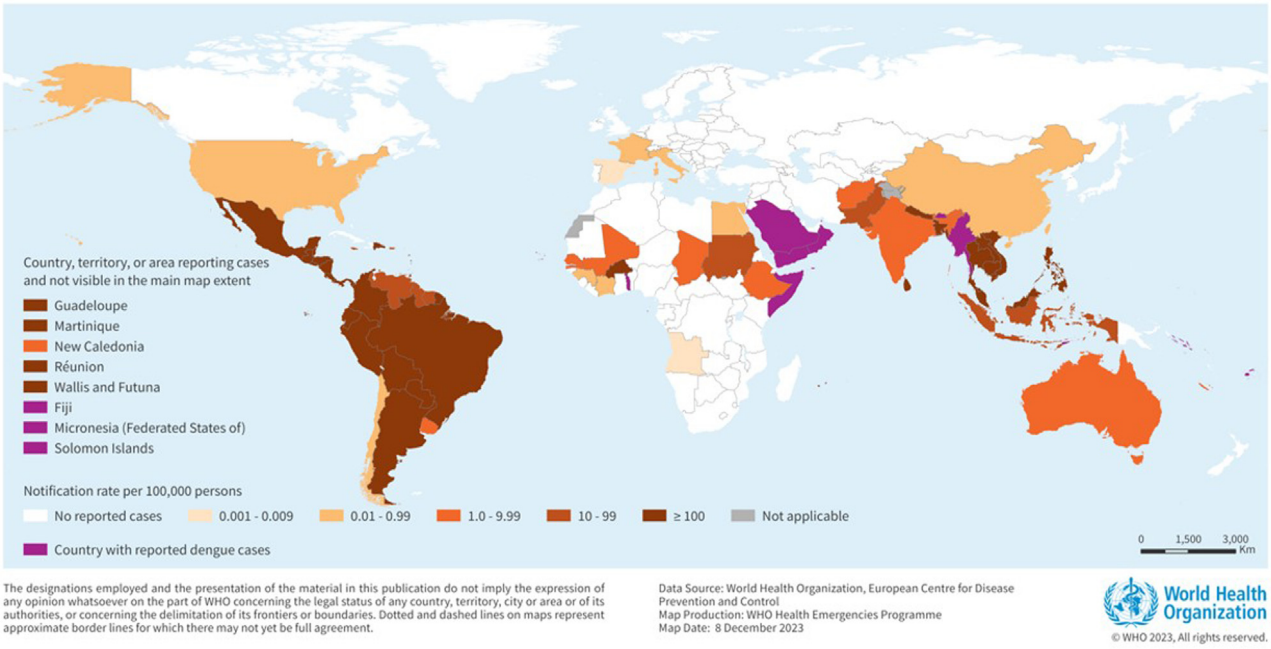

Fig. 1. Countries, territories, and areas reporting autochthonous dengue cases, November 2022–November 2023. (Reproduced from the World Health Organization, Disease Outbreak News: Dengue – Global situation, 21 December 2023.)

orbital pain, myalgia, arthralgia, nausea, vomiting, diarrhoea, and occasionally a transient, often petechial, rash. Dehydration is common because of poor oral intake or gastrointestinal losses. These symptoms often prompt patients to seek medical attention. Early blood counts may be normal or show leukopenia and thrombocytopenia.

Critical phase

The critical phase typically coincides with defervescence around days 3–7 and lasts 24–48 hours. Fever resolution, progressive leukopenia with relative lymphocytosis, and a rapid decline in platelets to nadir

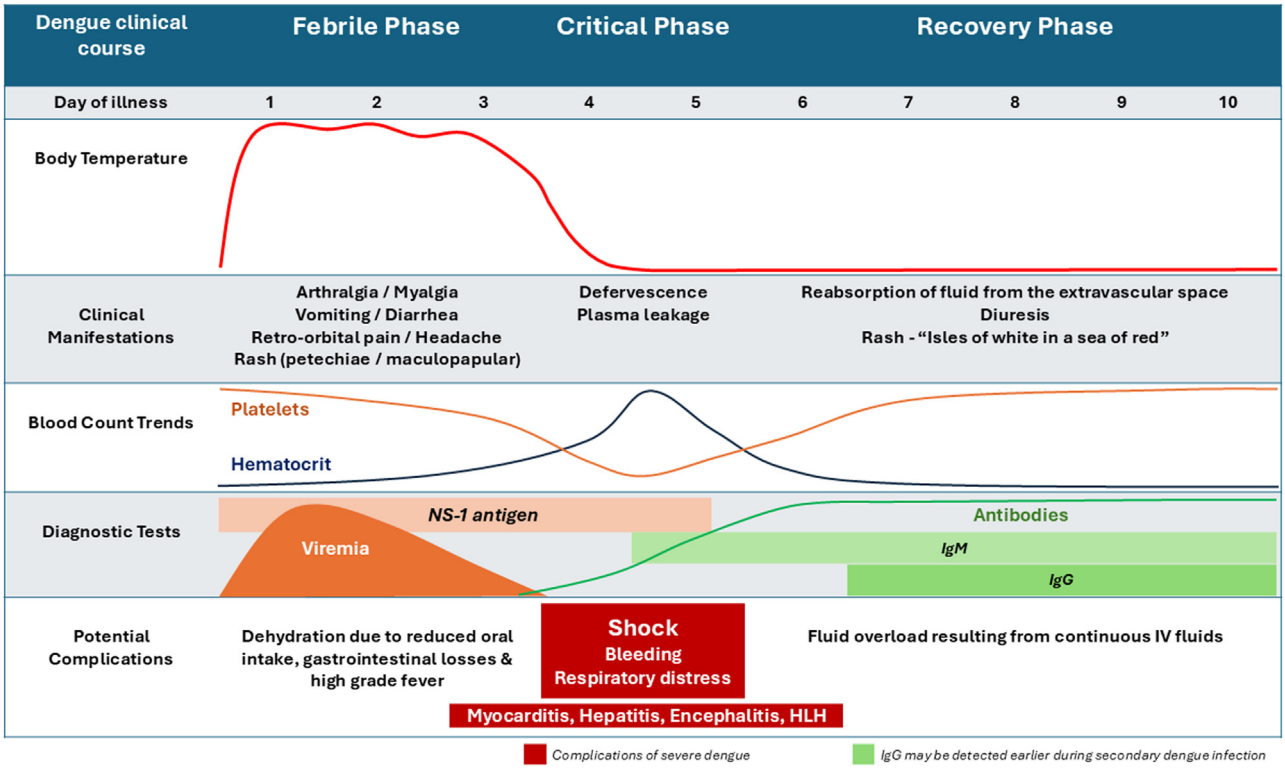

Fig. 2. Overview of dengue clinical phases with corresponding clinical features and potential complications.

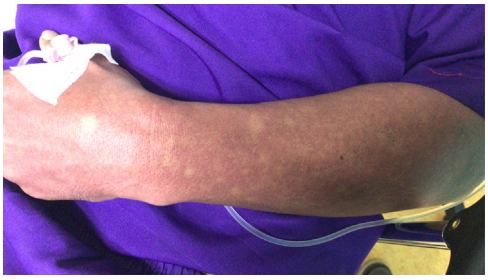

Fig. 3. Characteristic rash 'isles of white in the sea of red' which appeared in a patient during dengue recovery phase. (Patient consent obtained for use of this image.)

indicate the onset of this high-risk period [15]. Patients may appear to improve as fever and other debilitating symptoms subside, but this apparent recovery can be misleading, as the hallmark pathophysiology of severe dengue, plasma leakage, may occur. Importantly, severe dengue is frequently preceded by warning signs [14,16].

Plasma leakage leads to haemoconcentration, often marked by a haematocrit rise ≥20% above baseline and fluid accumulation in interstitial or serosal spaces. Without adequate fluid replacement, it can progress to hypovolemic shock with tissue hypoperfusion, metabolic acidosis, and hyperlactatemia. Prolonged shock may cause severe overt or occult bleeding. Other complications beyond plasma leakage include severe hepatitis, cardiac dysfunction, renal failure, encephalitis, and haemophagocytic lymphohistiocytosis (HLH), a life-threatening hyperinflammatory syndrome characterized by a cytokine storm [14,17,18].

Recovery phase

The recovery phase follows if the patient safely navigates the 24–48-hour critical phase. It is marked by reabsorption of extravascular fluid, diuresis, clinical improvement, and gradual normalization of white blood cells and platelets [14]. Some patients may develop a rash described as 'isles of white in a sea of red', often accompanied by pruritus (Fig. 3).

Warning signs and severe dengue

In 2009, WHO introduced a revised dengue classification, replacing the traditional categories of dengue fever and dengue haemorrhagic fever with three risk groups: dengue without warning signs, dengue with warning signs, and severe dengue (Fig. 4). Warning signs that herald progression to severe dengue include abdominal pain or tenderness, persistent vomiting, lethargy or restlessness, clinical fluid accumulation (ascites or pleural effusion), mucosal bleeding (e.g. gums, nose, vaginal), liver enlargement >2 cm below the costal margin, and a rising haematocrit with a rapid drop in platelet count [14]. This classification framework reflects disease progression, identifies high-risk patients, and guides appropriate intervention and escalation of care [19].

Severe dengue is defined by severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment, such as hepatitis (aspartate aminotransferase/alanine aminotransferase [AST/ALT] >1000 U/L), myocarditis, renal failure, and encephalitis [14]. A study of 271 patients with severe dengue in Latin America and Asia found that 90% had severe plasma leakage (more common in children and adolescents), 14% had severe bleeding, and 10% had severe organ dysfunction [20].

Microbiology, immunology, and pathogenesis

The pathogenesis of dengue reflects a complex interplay between viral factors and host immunity. DENV comprises four antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. A primary infection with one serotype typically induces protective, serotype-specific neutralizing antibodies.

During a secondary infection with a different serotype, persistent heterotypic antibodies from the primary infection may bind to the virus without neutralizing it. These antibodies form complexes that facilitate viral entry into Fc receptor–bearing monocytes and macrophages, a process known as antibody-dependent enhancement (ADE). ADE is strongly implicated in severe dengue, as it amplifies viral replication, increases viraemia, and heightens proinflammatory responses. Viral nonstructural protein 1 (NS1), together with elevated cytokines (e.g. TNF-α, IL-6, IFN-γ), complement activation, platelet-activating factor, and leukotrienes, disrupts endothelial junctions and degrades the glycocalyx, resulting in increased vascular permeability and plasma leakage [21,22].

At the population level, shifts in predominant circulating dengue serotypes often precede major outbreaks by increasing the risk of severe secondary infections. Understanding dengue viral evolution and population immunity can help predict epidemic timing, magnitude, and severity [9,23].

Differential diagnosis and diagnostic work-up

In endemic tropical countries, acute febrile illnesses are a leading cause of clinic and hospital visits. The differential diagnosis is broad, encompassing viral, bacterial, and parasitic infections. Common dengue symptoms such as high fever, headache, myalgia, arthralgia, diarrhoea, and rash overlap substantially with other arboviral infections, including chikungunya and Zika. Chikungunya typically presents with more prominent and prolonged arthralgia, whereas Zika infection is often milder and may feature conjunctivitis and a pruritic rash. In regions where these viruses cocirculate, clinical features alone are insufficient for reliable differentiation [24,25].

In South and Southeast Asia, dengue is the leading cause of acute undifferentiated febrile illness, accounting for 16.6% of adult and 18.7% of paediatric patients, followed by leptospirosis, typhoid, scrub typhus, other rickettsial diseases, and malaria [26]. These tropical infections, as well as early COVID-19 and influenza, can mimic dengue in the febrile phase, creating diagnostic uncertainty. Misdiagnosing leptospirosis or typhoid as dengue may delay antibiotics, whereas missing early dengue can lead to unnecessary antibiotics and suboptimal fluid management. Timely, reliable point-of-care testing is therefore essential for effective case management and public health surveillance in dengue-endemic regions [27].

In suspected dengue, point-of-care NS1 antigen detection is most useful within the first 5 days of illness. Beyond day 5, IgM and IgG serology are more reliable as antibody responses develop [28,29]. In secondary infections, IgG rises early and rapidly to high titres, whereas IgM may be low, delayed, or absent (Fig. 2). Combining NS1 antigen and IgM in rapid diagnostic tests provides up to 99.1% sensitivity and 100% specificity, enabling accurate dengue detection from the acute to the convalescent phase [30]. RT-PCR is highly specific for acute infection but is limited in clinical practice by cost and longer turnaround times, and is typically reserved for surveillance or research.

Recommended treatment and monitoring

Initial dengue management focuses on symptomatic relief, maintaining adequate oral hydration, and ensuring good urine output (>0.5 mL/kg/h). Paracetamol is recommended for fever and pain, with caution in patients with dengue-associated hepatitis. Nonsteroidal anti-inflammatory drugs and aspirin should be avoided because of the increased risk of bleeding [14,31].

Most patients can be safely managed at home or as outpatients with daily monitoring of blood counts and vital signs. However, without effective therapeutics, early identification of the 3–5% of symptomatic patients at risk of progression to severe dengue is crucial, as they may

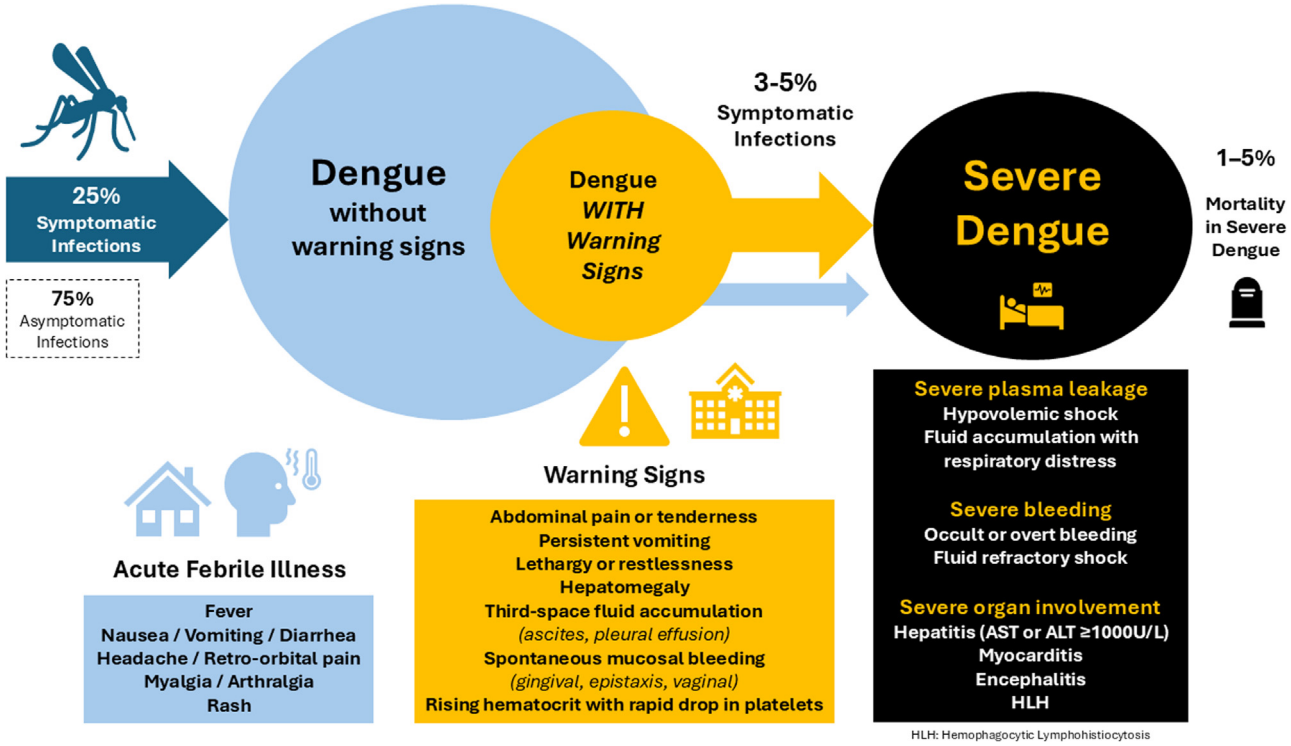

Fig. 4. Clinical classification of dengue, illustrating the spectrum of illness. Patients with warning signs are more likely to progress to severe dengue. This classification guides clinicians in determining the appropriate level of care and monitoring. (Adapted from WHO Dengue Guidelines 2009 and Malaysian Clinical Practice Guidelines for Management of Dengue Infection in Adults 2015.)

require hospitalization for close monitoring and timely intervention in case of deterioration [13,19]. This poses a major challenge during outbreaks, when healthcare capacity is often overwhelmed. Although comorbidities (diabetes mellitus, renal failure, cardiovascular disease, obesity), pregnancy, advanced age, and infancy increase the risk of severe outcomes, early risk stratification remains limited by the lack of sensitive and specific biomarkers predictive of severe dengue.

A prospective study in Thailand identified three independent predictors of plasma leakage: body mass index ≥25 kg/m^2, platelet count <100 000/mm^3, and AST or ALT ≥100 U/L on days 3–4 [32]. A Sri Lankan study found that severe vomiting, diarrhoea, abdominal pain, and liver tenderness were associated with plasma leakage, but only liver tenderness on day 3 remained an independent predictor after adjustment (specificity 93%, sensitivity 44%) [33].

The WHO 2009 warning signs help identify patients at risk of severe dengue, but individual signs alone have low positive predictive value. Lethargy, abdominal pain or tenderness, and mucosal bleeding are common but relatively nonspecific [16]. In particular, lethargy is frequently observed in the febrile phase and does not necessarily indicate progression to severe dengue. Overreliance on these signs for admission or prolonged intravenous (IV) fluids can result in unnecessary hospitalization and fluid overload. Predictive accuracy improves when multiple warning signs are interpreted alongside clinical phase, haematocrit trends, and haemodynamic status (Fig. 5).

In Malaysia, hospitalization is recommended for patients with warning signs, poor oral intake, dehydration, shock, or organ failure. Special populations—elderly (>65 years), pregnant women, people with comorbidities, those on antiplatelets or anticoagulation, or with social factors limiting follow-up—also warrant admission [31].

Principles of fluid management and pitfalls

Dengue fluid management should be tailored to the febrile, critical, and recovery phases, as fluid requirements and risks vary. When indicated, IV fluids should be given at the minimum required to maintain perfusion, guided by clinical status, oral intake, urine output, haematocrit trends, and warning signs, while avoiding fixed high-volume drips to prevent overload [19,31,34] (Fig. 5).

During the febrile phase, oral hydration is prioritized. IV crystalloids such as normal saline are reserved for patients with poor intake, significant losses, or severe dehydration. Maintenance IV fluids are weight based, using the Holliday–Segar formula or the 1.2–1.5 mL/kg/h approach recommended by Malaysian adult dengue guidelines [31,34]. Indiscriminate IV fluid use in stable febrile patients can cause intravascular congestion and exacerbate plasma leakage during the critical phase (Fig. 6).

The critical phase requires vigilant management, as plasma leakage often begins at defervescence. IV fluids should be given only to patients with warning signs or haemodynamic instability. In those with warning signs but no shock, fluids can be administered as graded boluses from 5 mL/kg/h, tapering stepwise to 3 then 2 mL/kg/h, before reaching maintenance, and discontinued once warning signs resolve [31].

Inpatients should have at least twice-daily clinical review, with serial blood counts every 4–12 hours, vital signs every 2–4 hours, and urine output monitoring [31]. Peripheral perfusion should always be assessed at the bedside following the CCTVR mnemonic (skin colour, capillary refill time, extremity temperature, pulse volume, and pulse rate) to detect early hypovolemic shock. Point-of-care ultrasound can detect signs of plasma leakage, including ascites, pericholecystic fluid, gallbladder wall thickening (>3 mm), and pleural effusion, which can also be seen on chest X-ray [35].

Common pitfalls include delayed recognition of shock, overzealous fluid therapy leading to pulmonary oedema and respiratory distress, and missed occult bleeding. Thrombocytopenia and coagulopathy do not predict bleeding in dengue, whereas prolonged shock is the main risk factor for severe haemorrhage [36]. Prophylactic platelet transfusions are not recommended, as they offer no clinical benefit and may worsen fluid overload [14,31,37,38].

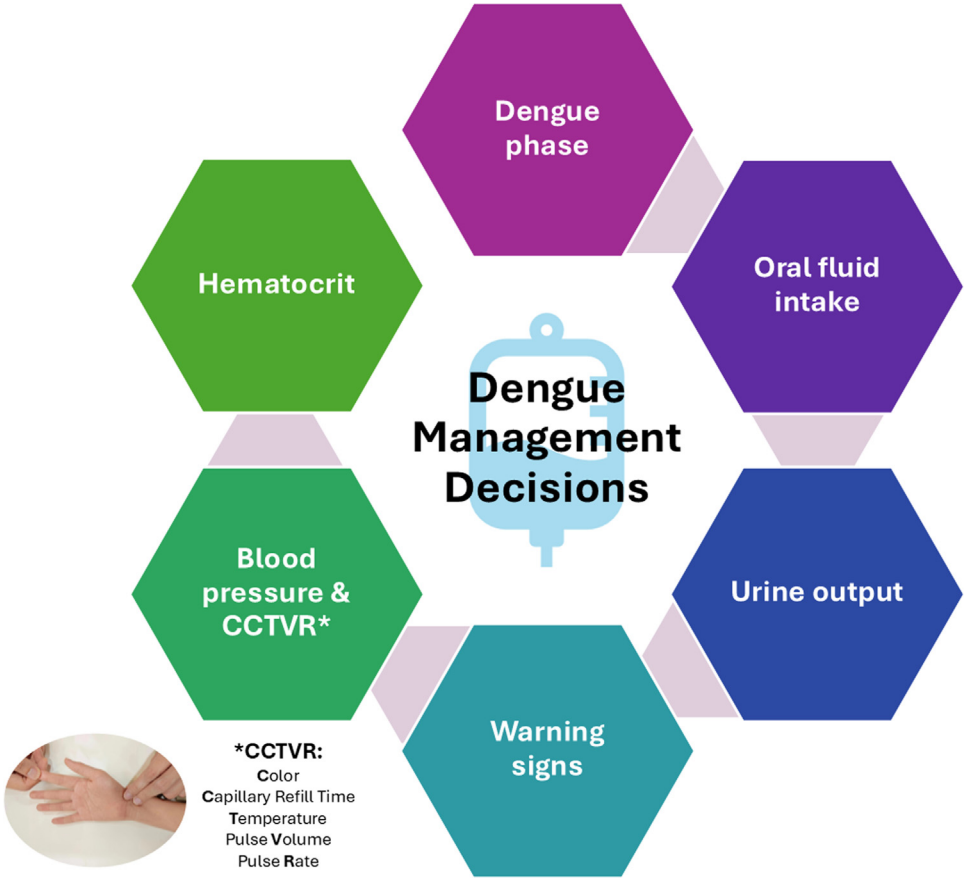

Fig. 5. A holistic approach to clinical parameters for dengue management decisions.

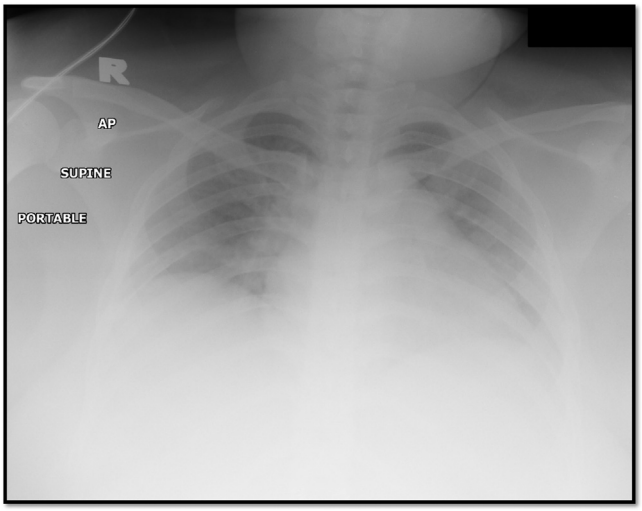

Fig. 6. A 23-year-old woman with obesity (body mass index 45.3) presented on day 3 of dengue (febrile phase) with lethargy and abdominal pain. Despite stable haemodynamics and no rise in haematocrit, she received repeated intravenous crystalloid boluses totalling 5.5 L over 11 hours, resulting in a positive fluid balance >3.0 L (urine output 2.15 L). As she entered the critical phase, she developed severe plasma leakage, culminating in acute pulmonary oedema and respiratory distress.

Once in the recovery phase, IV fluids should be stopped promptly as extravascular fluid is reabsorbed into the intravascular compartment. Continuing fluids may impede reabsorption and increase the risk of fluid overload. Patients can be discharged when clinically stable.

Management of severe dengue

Dengue shock syndrome (DSS) is a physiologic continuum. Unlike septic shock, which presents with marked systemic inflammation and early mental status changes, patients in early compensated DSS may appear deceptively stable, with normal consciousness and preserved systolic blood pressure. Recognizing subtle signs—tachycardia, cool extremities, delayed capillary refill, narrowing pulse pressure, and reduced urine output—is vital.

IV isotonic crystalloid resuscitation at 10 mL/kg/h should be initiated promptly, with hourly assessment of fluid responsiveness. Blood should be cross-matched in anticipation of bleeding after prolonged shock. If patients fail to respond or progress to decompensated hypovolemic shock, the fluid rate can be increased to 20 mL/kg as a bolus over 15–30 minutes [31,34] (Fig. 7).

In severe, refractory shock from massive plasma leakage, colloids or albumin may be used to maintain intravascular volume, although high-quality evidence for their superiority over crystalloids is lacking [31,39]. Colloids can restore cardiac index and reduce haematocrit faster than crystalloids in DSS [40], but risks of dextran or hydroxyethyl starch, including anaphylaxis and acute kidney injury, may outweigh the benefits. Notably, a study in Vietnam found that excessive fluid resuscitation and a high colloid-to-crystalloid ratio (≥1.6) in the first 24 hours were associated with mechanical ventilation in children with DSS [41]. Vasopressor use in DSS is also largely empiric, with short-term noradrenaline for fluid-refractory shock, whereas the inotrope dobutamine is considered when myocardial depression is present.

Shock with worsening metabolic acidosis unresponsive to fluids should raise suspicion of occult bleeding, with clues including a falling or inappropriately normal haematocrit (unlike the haemoconcentration seen in severe plasma leakage). Early transfusion with packed red blood

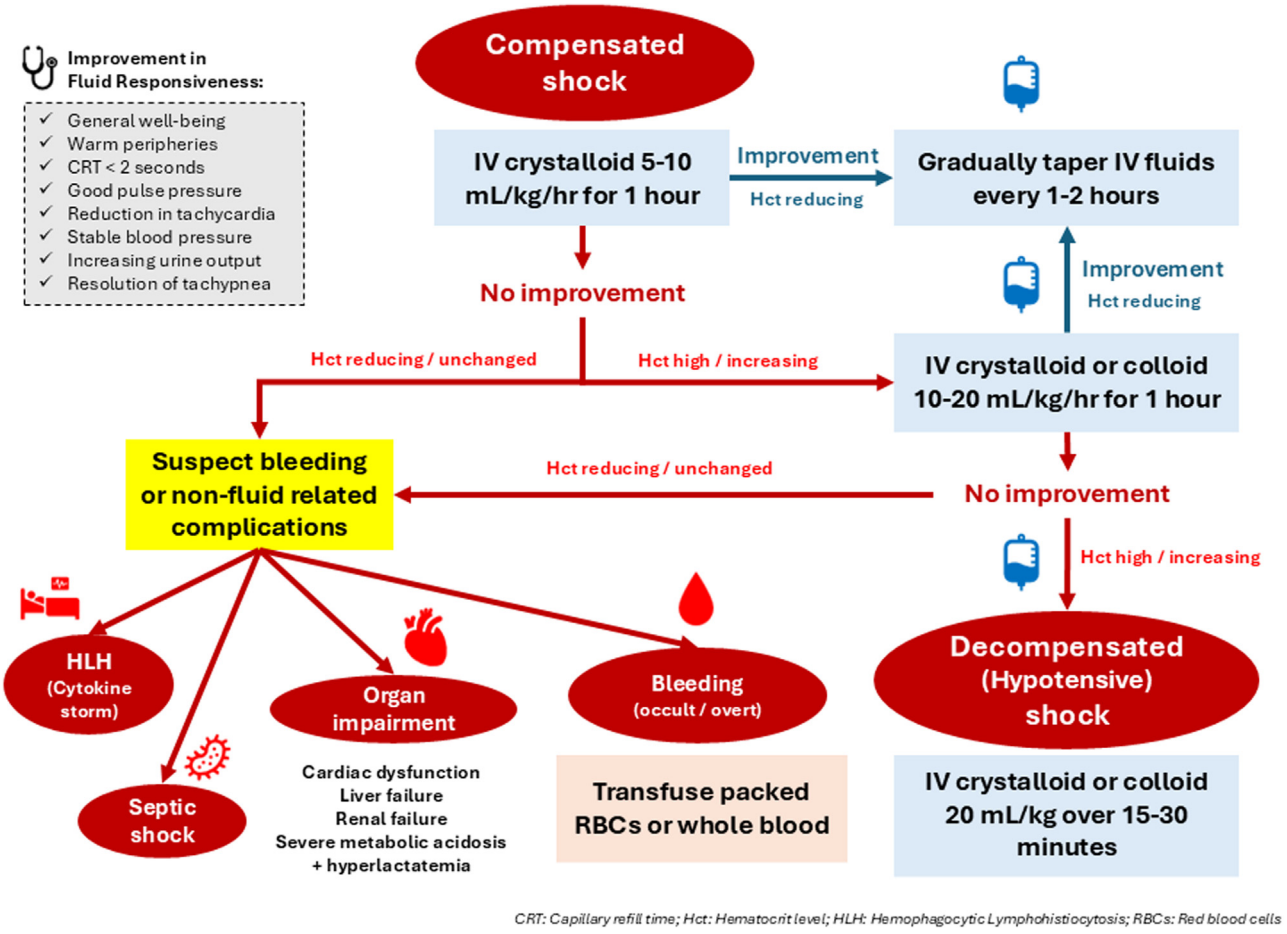

Fig. 7. Management algorithm for severe dengue.

cells (5–10 mL/kg) or whole blood (10–20 mL/kg) is vital to restore circulating volume and oxygen-carrying capacity [31] (Fig. 7).

Persistent critical illness in dengue should also prompt evaluation for underlying organ impairment (Fig. 7). DENV typically invades the liver, causing hepatocyte apoptosis, which may be exacerbated by plasma leakage and immune-mediated injury. Dengue hepatitis with ALT/AST >500 U/L and/or an elevated international normalized ratio (INR) >1.5 may be treated with N-acetylcysteine infusion to hasten recovery [42]. Myocarditis affects an estimated 21% of patients with dengue, with higher rates in severe cases, potentially leading to cardiac dysfunction requiring inotropic support [43]. Unexplained arrhythmias or elevated cardiac enzymes should prompt evaluation with electrocardiogram and echocardiography. Dengue encephalitis may manifest with headache, altered consciousness, or seizures, but is usually self-limiting and managed supportively. Dengue-associated secondary HLH often presents with fever >7 days, severe or refractory cytopenias, hyperferritinemia, and severe liver impairment. Diagnosis is based on HLH-2004 criteria or HScore. Severe cases with multiorgan involvement may receive a short course (3–4 days) of high-dose corticosteroids, such as dexamethasone 10 mg/m^2/d [18,44].

Clinical considerations in high-risk populations

Pregnancy causes plasma volume expansion, particularly in the second and third trimesters, which can mask haematocrit rises from plasma leakage, whereas the gravid uterus may obscure ascites or pleural effusion. Patients with heart failure or chronic kidney disease have a narrow margin between hypovolemic shock and fluid overload, necessitating individualized IV therapy at slower rates, careful haemodynamic monitoring (including point-of-care ultrasound), and judicious diuretic use. In diabetes mellitus, strict glycemic control is essential to prevent osmotic diuresis, which complicates urine output monitoring and worsens hypovolemia, whereas persistent hyperglycemia increases the risk of diabetic ketoacidosis and secondary infections.

Prevention and closing knowledge gaps

Vector control remains the cornerstone of dengue prevention. Unlike nocturnal, malaria-transmitting *Anopheles* mosquitoes, *Aedes* mosquitoes bite during the day, peaking at dawn and dusk. Bed nets used during sleep are therefore less effective. Repellents, protective clothing, and elimination of standing water breeding sites remain standard preventive measures. Despite public health efforts, including targeted fogging, community engagement, and environmental management, the continued escalation of the global dengue burden underscores the urgent need for innovative and sustainable control strategies. Notably, partial replacement of wild *A. aegypti* populations with Wolbachia-infected mosquitoes effectively blocks dengue transmission. In Malaysia, field releases of Wolbachia-infected *A. aegypti* in dengue hotspots have reduced dengue cases by an average of 62.4% [45].

Vaccination represents a major breakthrough in dengue prevention. However, the first licensed dengue vaccine, Dengvaxia (CYD-TDV), increased the risk of severe dengue in seronegative recipients via ADE, where vaccination mimics a primary infection and predisposes to severe disease on subsequent natural infection [46]. In contrast, QDenga (TAK-003), a recently approved live-attenuated tetravalent dengue vaccine, demonstrated 61.2% efficacy against virologically confirmed infection and 84.1% efficacy against dengue-related hospitalization over 4.5

years, with no evidence of increased severe disease risk among seronegative recipients [47]. Prevaccination serostatus screening for QDenga is generally not required, although certain countries, such as the United Kingdom, recommend it only for seropositive individuals as a precaution [48].

Early dengue therapeutics remain a critical unmet need. Antivirals that significantly reduce viraemia, and host-directed therapies that modulate the inflammatory response to prevent plasma leakage, should ideally be initiated within the first 72 hours of illness. Early therapeutic intervention could prevent progression to severe disease, reduce the need for intensive monitoring and hospital admission, and protect vulnerable healthcare systems during dengue surges. Industrial interest and investment in dengue therapeutics remain limited, and candidate treatments are few, as the disease predominantly affects the Global South. To address this gap, the Dengue Alliance, a Global South–South research collaboration involving dengue-endemic countries such as Brazil, Malaysia, Thailand, and India, was established in 2022 to accelerate the therapeutic development [49]. Concurrently, predictive biomarkers for severe dengue are urgently needed to improve risk stratification and identify patients most likely to benefit from therapeutic interventions.

Conclusion

The dengue burden continues to rise worldwide. The WHO aims for zero dengue deaths globally by 2030 [50], a target attainable only through enhanced surveillance, effective vector control, broad and accessible vaccination coverage in endemic countries, and robust case management. Although early diagnosis, risk stratification, close monitoring, and judicious fluid management remain essential, urgent research into dengue therapeutics and biomarkers is needed to further reduce morbidity and mortality.

Self-quiz

See last section for answers

1. Which of the following is a warning sign of severe dengue?
   A. Petechial rash
   B. Abdominal pain
   C. Retro-orbital pain
   D. Arthralgia

2. Which of the following is NOT true regarding the dengue critical phase?
   A. High spiking fever
   B. Progressive leukopenia and thrombocytopenia
   C. Plasma leakage may present with a rising haematocrit ≥20% from baseline
   D. Typically lasts up to 48 hours

3. Which of the following patients with dengue warrants IV fluid administration?
   A. High-grade fever during the febrile phase with mild dehydration but able to maintain oral intake
   B. Appears lethargic during the febrile phase but able to maintain oral intake with good urine output
   C. Persistent vomiting and abdominal pain after defervescence, with a rising haematocrit
   D. Afebrile for more than 48 hours, asymptomatic, with gradual recovery of white blood cells and platelets

4. In a patient with dengue shock receiving fluid resuscitation, which of the following findings should prompt suspicion for occult bleeding?
   A. Falling haematocrit without clinical improvement
   B. Persistent shock despite repeated fluid boluses
   C. Worsening metabolic acidosis
   D. All the above

Declaration of competing interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Steven Chee Loon Lim: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Hiu Jian Chua:** Writing – review & editing.

Answers for Self-Quiz

1. B
2. A
3. C
4. D

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